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Hylonome

Clinical Quiz

Coexistence of Paget disease of bone and primary hyperparathyroidism; a diagnostic challenge

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Case

A 74-year-old man visited our orthopaedic outpatient clinic complaining about pain of the right hip. The pain was mild, but constant, even at night, had risen gradually during the month prior to his visit and was not causing limping. No history of trauma was reported and the patient was otherwise healthy. Plain radiographs of the pelvis and hips demonstrated a large dense area at the right anonymous bone (Figure 1A). An extensive radiologic and laboratory survey including computed tomography (CT) of the pelvis and hips and bone scintigraphy with technetium-99m followed (Figures 1B and 1C). Excessive radionuclide uptake was noticed at the right anonymous bone but, also, at the fourth and fifth lumbar vertebras. CT of the lumbar spine confirmed that the lesions in spine were degenerative.

In addition, the patient underwent laboratory investigation with blood and urinary tests. Serum bone alkaline phosphatase was high (BALP 83.9 μg/lt; normal reference values (rv) <20.1 μg/lt), with total alkaline phosphatase (ALP) 199.0 IU/lt (rv 40-129 IU/lt), but osteocalcin and CTX were normal (29.4 ng/ml, rv 11-46 ng/ml and 0.723 ng/ml, rv<0.84 ng/ml, respectively). All other tests were normal, with the exception of parathyroid hormone (PTH) that was found elevated (86.9 pg/lt; rv 15-65 pg/ml), with serum calcium (Ca) 9.1 mg/dl (rv 8.2-10.2 mg/dl), serum phosphate (P) 2.8 mg/dl (rv 2.7-4.5 dg/ml), 25(OH)vitamin D_3 22.1 ng/ml [rv>20 ng/ml, according to the Institute of Medicine (IOM)'s and the European Society of Endocrinology (ESE)'s suggestions] and 24-hour urinary Ca levels 224 mg/24h (rv 100-300 mg/24h). On reviewing past laboratory exams ALP was found to be elevated in repeated measurements during the previous five years.

Based on the radiologic and laboratory findings, the patient was diagnosed with Paget disease of bone (PBD). We considered that PTH levels were inappropriate for the serum Ca levels and in the absence of secondary causes of hyperparathyroidism we considered the diagnosis of normocalcemic primary hyperparathyroidism. Further investigation with ultrasonography (US) of the thyroid and parathyroid glands revealed multinodular goiter and a hypoechoic mass (1.36 X 0.44 cm) with moderate vascularization located behind the upper pole of the left thyroid lobe indicative of adenoma of the upper left parathyroid gland. The patient was referred for parathyroidectomy and total thyroidectomy. Biopsy confirmed the diagnoses (Figure 2). Calcium and vitamin D supplements as well as thyroid hormone replacement therapy and a single intravenous infusion of 5 mg zoledronic acid were administered following surgery. Three months postoperatively the patient's symptoms had subsided and serum ALP, PTH, Ca and P were within normal range (84 IU/lt, 32 pg/lt, 9.0 mg/dl and 3.7 mg/dl, respectively).

Commentary

PBD is relatively common in Europe, Australia, Canada, New Zealand, South Africa, and the United States with up to 3% of people above the age of 50 suffering from the disease. PHPT is one of the most common endocrine diagnoses and is caused by a single parathyroid adenoma in 75-85% of cases. Both diseases affect the skeleton, alter bone turnover and can

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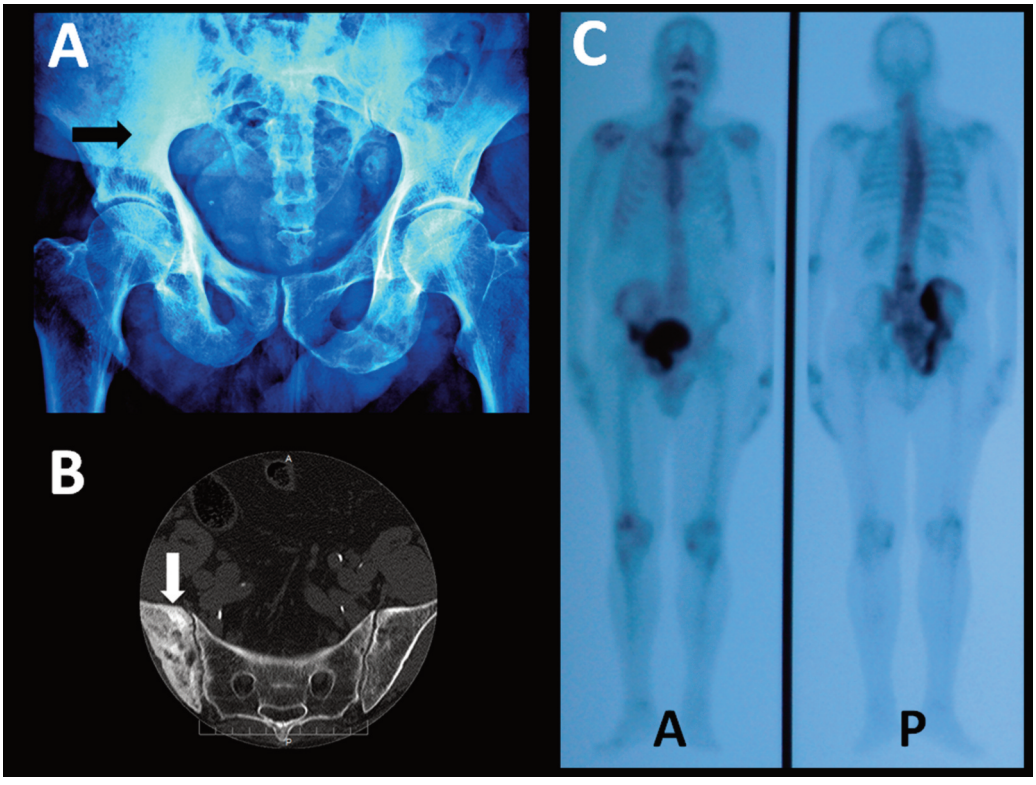

Figure 1. A) Anteroposterior X-ray of the pelvis shows a large dense area at the right anonymous bone (black arrow). **B)** Abnormal imaging (thickening of the cortices and osteosclerosis of the trabecular bone) of the right anonymous bone in computed tomography of the pelvis (white arrow). **C)** Bone scintigraphy with technetium-99m. Excessive radionuclide uptake at the right anonymous bone. [(A) anterior view, (P) posterior view].

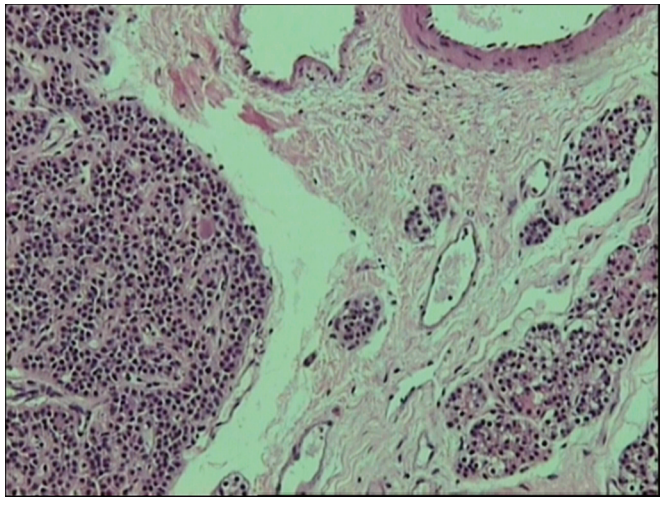

Figure 2. Adenoma of the upper left parathyroid gland as seen in histologic preparation.

produce bone pain, fractures and deformities so their coexistence poses a diagnostic challenge to the clinician.

PBD is characterized by focal areas of increased bone turnover in one or more skeletal sites that is primarily caused by disturbance in osteoclast differentiation and function. The disease preferentially affects the axial skeleton, and the most common sites involved are the pelvis, femur, lumbar spine, skull and tibia. Most patients are asymptomatic and only about 30% present clinical signs. Bone pain is the commonest manifestation. Deformities of the affected bones, increased skin temperature over the pathologic areas, fractures that occur even with minor trauma and cranial nerve compression syndromes can also be detected. Diagnosis is predominately based on the radiologic and biochemical findings and bone biopsy is seldom necessary (in cases where differential diagnosis is confusing). Common appearance in plain radiographs consists of combinations of the following: expansion of affected bones, irregular condensation with a fibrillar or mottled appearance, osteolytic areas and loss of the clear-cut limit between cortical and trabecular bone. The differential diagnosis includes hyperostosis frontalis interna, fibrous dysplasia, pustulotic arthrosteitis and osteosclerotic metastases.

The biochemical profile of PBD patients varies and depends on the phase (lytic, intermediate, sclerotic) and the form

(polyostotic, monoostotic) of the disease. Serum ALP is elevated in 95% of untreated patients, but normal concentrations can be found in monoostotic or metabolically inactive disease. In most cases ALP is sufficient for monitoring the activity of PBD and the response to treatment. Serum Ca and P are usually normal with the exception of immobilization of PBD patients that can cause hypercalcaemia. On the other hand, serum magnesium levels can be low, especially in the older patients. Biochemical markers of bone resorption and formation are often elevated following the activity of the disease.

Increases of serum PTH are found in 12-18% of patients with PBD[1]. In the vast majority of cases elevation of PTH is attributed to secondary hyperparathyroidism caused by increased Ca demands during the bone producing phases of PBD, vitamin D deficiency or insufficiency, antiresorptive treatment (e.g. with bisphosphonates), low Ca intake or a combination of the above. Adenoma or hyperplasia of the parathyroid glands is discovered rarely in patients with PBD. The estimated prevalence is 2.2-6.0% based on large PBD cohorts[2,3] with more women being affected than men (female: male=2.75:1 [2], female: male=3.57:1 [3]). Comparison with the prevalence and sex distribution of PHPT in the general population (about 3% of women and 1% of men over 60 years old) suggests that there is no aetiologic linkage between the two disorders. However, the fact that *SQSTM1 gene*, which is involved in the pathogenesis of PBD, and *multiple endocrine neoplasia type 1 (MEN 1) gene*, which is involved in the pathogenesis of PHPT, share the same signaling pathway through Nuclear Factor kappa Beta indicates that there is a possible connection among PBD and PHPT[4].

PHPT is characterized by elevated or inappropriately normal PTH levels and biochemical markers of bone turnover are altered usually in favor of bone resorption. Its classical form is characterized by hypercalcaemia, nephrolithiasis, generalized bone disease with low bone mineral density, "brown tumors", fractures and bone pain, neuropsychiatric manifestations, and increased cardiovascular risk. However, most patients in our days are asymptomatic. The most likely explanation for the shift in clinical presentation is a more extensive screening for the disease based on routine serum Ca measurements. In addition, it is clear now that another entity, normocalcemic hyperparathyroidism (NHPT), exists. As in our patient, NHPT is characterized by consistently normal Ca concentrations and persistently elevated PTH levels[5].

There is no consensus about the criteria for parathyroidectomy in patients with both disorders. It is reported that surgery improves their biochemical profile and symptoms[2]. A thorough discussion with the patient about the potential advantages and disadvantages should be made before any action. Our patient's decision to undergo parathyroidectomy (in combination to a single intravenous infusion of zoledronic acid 5 mg) led to impressive clinical improvement at the follow up three months postoperatively. Also, serum ALP, PTH, Ca and P were within normal range confirming the success of the treatment.

In conclusion, investigation of bone metabolism parameters is of absolute necessity when dealing with patients with PBD as a means of monitoring the activity of the disease, the response to treatment and identification of other underlying bone pathologies. A thorough evaluation should include measurements of serum ALP, Ca, P, PTH, 25(OH)vitamin D_3 and biochemical markers of bone turnover in addition with 24-hour urinary Ca. In patients with elevated PTH levels and normal or high serum Ca, secondary causes of hyperparathyroidism should be ruled out. In the absence of secondary hyperparathyroidism, PHPT is the predominant diagnosis and should be confirmed by ultrasonography and treated appropriately.

References

1. Siris ES, Clemens TP, McMahon D, et al. Parathyroid function in Paget's disease of bone. J Bone Miner Res 1989;4:75-9.
2. Gutteridge DH, Gruber HE, Kermode DG, et al. Thirty cases of concurrent Paget's disease and primary hyperparathyroidism: sex distribution, histomorphometry, and prediction of the skeletal response to parathyroidectomy. Calcif Tissue Int 1999;65:427-35.
3. Posen S. Paget's disease: current concepts. Aust N Z J Surg 1992;62:17-23.
4. Brandi ML, and Falchetti A. What is the relationship between Paget's disease of bone and hyperparathyroidism? J Bone Miner Res 2006;21(Suppl.2):P69-74.
5. Shlapack MA, and Rizvi AA. Normocalcemic primary hyperparathyroidism-characteristics and clinical significance of an emerging entity. Am J Med Sci 2012; 343:163-6.

Questions

1. Which of the following is false?
A. PBD primarily affects the osteoclasts
B. PHPT is always characterized by elevated or inappropriately normal PTH levels and hypercalcaemia
C. None of the above

Critique

PBD is caused by disturbance in osteoclast differentiation and function. Usually, PHPT is characterized by elevated or inappropriately normal PTH levels and hypercalcaemia but nowadays many patients present with consistently normal Ca concentrations and persistently elevated PTH levels (normocalcemic hyperparathyroidism).
The correct answer is B.

2. In patients with PBD elevation of PTH is usually associated with
A. Adenoma or hyperplasia of the parathyroid glands
B. Secondary hyperparathyroidism
C. None of the above

Critique

Elevated serum PTH is found in approximately 12-18% of patients with PBD, while PHPT in only 2.2-6.0% of patients with PBD. In most cases PTH rise is attributed to secondary causes such as increased Ca demands during the bone producing phases of PBD, vitamin D deficiency or insufficiency, antiresorptive treatment, low Ca intake or a combination of the above.
The correct answer is B.